Therapeutic Cannabidiol Pulmonary Delivery Device (e.g. Nebulizer, Vaporizer or Inhaler)

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The official link for this solicitation is: https://sbir.nih.gov/sites/default/files/PHS2016-1.pdf

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Description:

Objective

To develop a pulmonary delivery device that can administer therapeutic doses of the non-psychoactive cannabinoid CBD. The ultimate goal is to generate a sufficiently characterized clinical tool such that the Food and Drug Administration (FDA) would allow it to be used to evaluate the efficacy of inhaled CBD as a therapeutic agent in clinical trials.

This opportunity is open to all Small Business Innovation Research (SBIR) award-eligible organizations. However, it is anticipated that a Small Business Concern (SBC) best equipped to produce such a characterized device and data package within the time and budget constraints might currently be marketing a similar or related inhalation product.

Aspects of a Market analysis

The NIDA foresees a niche for the SBC with a pulmonary CBD delivery device that has previously successfully undergone Federal IND review. This product would be marketed to clinical researchers wishing to conduct clinical studies into potential therapeutic effects of CBD. The SBC would supply the researchers with devices and allow them to cross-reference the original IND in their own FDA

application(s). All proprietary information would be kept between the SBC and the FDA.

- **Diversified Income Stream-** Clinical researchers in the US (and beyond) represent limited / no-competition market niche, protected by the costs involved in characterizing the device and obtaining an IND.

- **In a market where designs are rapidly evolving** this representsa situation where a stable device design is prized and minimal future R&D investment will be required**.**

- **Informing Product Development-** Characterizing your existing product will aid future design efforts and perhaps "future-proof" against a scenario where greater regulatory oversight might require characterization.

- **"Free" Clinical Data Studies** The product would be described as a generic NIH device, butthe SBC would be welcome to reveal their involvement in NIH clinical studies in their marketing materials.

Background

CBD is a compound found in marijuana that has no euphoric properties but appears to have other pharmacological activities. Current understanding of CBD pharmacology is limited; a number of laboratory studies have been conducted and a few have progressed into early clinical phase investigations, the most successful demonstrating CBD as an anxiolytic agent. Potential applications for the anxiolytic properties of CBD include reduction of craving and relapse in Substance Use Disorders, and reduction of anxiety in Post-Traumatic Stress Disorder. In addition, CBD is currently under clinical investigation for the treatment of childhood intractable epilepsies, where it is added to the existing medication regimen (usually, to 2-3 other drugs). However, CBD is well known as an inactivator of drug metabolizing enzymes and so can significantly disturb the patient's exposure to their current medications and potentially contribute to serious drug interactions. If CBD is to be administered via a pulmonary (inhaled) mechanism rather than via oral route, the liver exposure would be much lower, resulting in less enzyme inactivation and drug-drug interactions. Furthermore, inhaled CBD provides 2-3x greater bioavailability and shows substantially lower inter-dose and inter-subject variability than with oral administration. when used in a clinical trial a pulmonary delivery device would result in more reproducible CBD dosing, less risk of drug interactions and ultimately less variable and more reproducible clinical data.

Project Overview

- The solicitation is open to all small businesses. SBCs with similar / related existing technologies are especially encouraged to apply.
- Products based on herbaceous material will not be acceptable, all formulations will need to be liquids or solids manufactured according to current Good Manufacturing Practices (cGMP).
- The delivery device could be in the form of a vaporizer, nebulizer, dry-powder inhaler or any other FDA-approvable pulmonary delivery device.
- Phase 1 of the project characterizes the quantity and reproducibility of CBD delivered in a single 5-second puff, as well as the identities and the amounts of all other agents in the vapor/aerosol.
- All components of the device and liquid are to be manufactured according to Good Manufacturing Practices (cGMP) or when such standards do not exist manufacturing should be performed according to the "spirit of GMP".
- Analytical Studies are to generate Certificates of Analyses demonstrating an appropriate and reproducible CBD output as well as quantities of all other emissions. Studies are to be conducted by an ISO 17025 laboratory.
- The Phase I deliverables also include the minutes of an FDA pre-IND submission meeting outlining FDA expectations for any additional studies / data that would be required for a successful IND application.
- If selected to progress into phase II, the SBC is to conduct the studies required by the FDA to achieve a successful IND to examine the pharmacokinetics of CBD delivery by the device in

normal healthy adults. In addition, in Phase II, a 10 person study would be conducted to evaluate the pharmacokinetics of single dose/session administration of CBD using the device. It is recognized that a pharmacokinetic study may not always require an IND, but a protocol is required for the FDA to consider the suitability of the data package for issuance of IND. Once the data package has been allowed for one study, that IND can then be cross-referenced in future studies.
- It is expected that the data from the pharmacokinetic study would be published in a peer reviewed journal).

- Phase II projects will also require elucidation of the strategy that will be used to move the proposed research tool to a marketable product. Evidence of a track record of commercialization and / or commitment of additional investment from private sector or other non-SBIR funding sources will be expected.

    - Phase II would consist of studies aimed to satisfy FDA requirements for issuing an IND and the conduct of a 10 person study to evaluate the pharmacokinetics of single dose/session administration of CBD using the device. It is recognized that a pharmacokinetic study may not always require an IND, but a protocol is required for the FDA to consider the suitability of the data package for issuance of IND.

- The SBC would agree to market this device as characterized (without further change) to all clinical researchers who have been granted NIH funds to conduct the relevant studies.

- The device would be available for a sufficient period after the completion of the project to allow clinical studies to be conducted (i.e. 5-10 y).

- The SBC would retain the proprietary data held within the Drug Master File but would allow NIH researchers (and other customers) to cross reference the original Investigational New Drug Application (IND) using that data in order when seeking FDA approval for their study.

    - The battery used in the device must be rechargeable using a USB port and not meet the definition of hazardous waste as described in 40 CFR 261, subpart C.
    - The device should deliver at least 40 mg CBD to the vapor / aerosol over 10 minutes of use
    - Availability of other formulations such as a placebo formulation would be desirable, but not essential. If several formulations are proposed, the budget may potentially be modified accordingly during the negotiation phase (if the government determines negotiations are necessary). A formulation that contains a defined low amount of THC in combination with the required CBD delivery would also be viable as an additional formulation, although NIDA would need to be the source of the THC during the course of the contract.
    - Phase II would consist of studies aimed to satisfy FDA requirements for issuing an IND and the conduct of a 10 person study to evaluate the pharmacokinetics of single dose/session administration of CBD using the device. It is recognized that a pharmacokinetic study may not always require an IND, but a protocol is required for the FDA to consider the suitability of the data package for issuance of IND.

The Phase I contract proposal must include:

- A description of the device appearance and characteristics, including (but not limited to)
    - The liquid reservoir volume
    - The device dimensions and weight
    - An image of the device
- Information regarding protections to prevent a user's exposure to the CBD containing liquid.
- Estimation of the number of puffs per cartridge, tank fill or disposable device (as appropriate)

using a defined puffing topography (see Phase I Activities and Expected Deliverables).
- Estimation of the number of 5 sec puffs on a single battery charge (where applicable). The number of times a battery can be discharged to less than 20% of full charge and then recharged to >90% of specified full charge (estimation of battery life) should be described.
- Estimation of device time to failure.
- Concentration of CBD in the liquid formulation(s).
- Indicate the differential characteristics of each formulation (if several formulations are planned).
- Describe and provide examples of the data output, if the device possesses a data recording capability (not a requirement).
- The number units developed under this contract that are anticipated to be supplied annually and an indication of number of related units sold in a similar market place over last 1-2 years
- Documentation regarding capability to provide the device for a minimum of 5 years after the end of the development contract.
- Demonstration of the knowledge and capability to provide cGMP reagents in the completed device (see Guidance for Industry Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients).
- The anticipated cost of the device and any required accessories such as cartridges or battery chargers (where applicable). Cost should also be described in terms of equivalence to a typical herbal extract / nicotine vaporizer as well as the cost over the lifetime of a single device.
- It is recommended (but not essential) to describe experience of the key investigators or organization in the development of marketing of similar products to that proposed in this project.
- Demonstration of manufacturing and supply chain stability, is strongly advised including letters of support where applicable.

Phase I Activities and Expected Deliverables

This phase focuses on characterizing the chemical and mechanical characteristics of the device, including:

- Number of puffs per cartridge, tank fill (as appropriate). This is to be determined using a standardized puffing topography: 10 sec per puff, 60 ml puff volume, 20ml/sec flow rate, 30 sec puff interval. Grantees should also describe and test the optimal puff topography for their device, if different.
- The approximate number of 10 sec puffs, using the standard puffing topography, on a single battery charge (where applicable).
- Analysis of device time to failure.
- Chemical and Manufacturing Control (CMC) information for filing a Drug Master File (DMF) with the FDA. Batch reproducibility will also be covered in the CMC. Data will be generated from an ISO 17025 accredited laboratory.
- Information to be included in the DMF should be in agreement with the following FDA guidelines:
    - Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances.
    - Guideline for the Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application.
    - Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products.
    - Guideline for Submitting Samples and Analytical Data for Methods Validation.
    - Guidance for Industry INDs for Phase 2 and Phase 3 Studies - Chemistry, Manufacturing, and Controls Information.
- List of ingredients and a Certificate of Analysis (CoA) for each liquid formulation. Constituents analyzed must include: CBD, other cannabinoids present, cannabinoid breakdown products and vehicle components, for example, ethanol, propylene glycol, glycerin, acrolein and

formaldehyde. Reproducibility of liquid constituents should be demonstrated for at least 3 consecutive lots
    - CoA will be generated from an ISO 17025 accredited laboratory.
    - CoA for the vapor /aerosol produced by the device using the standardized puffing topography. Data should show the amount of CBD in the inhalant collected from the first 10 puffs and the amounts of all constituents (above 1 µg) present in the vapor collected from the first 150 puffs.
    - Indicate highest temperature of vapor / aerosol exiting device during a standard puff.
    - Indicate aerosol droplet size range where appropriate.
    - Indicate variation in the vapor constituents over the lifetime of the device.
- Long term and accelerated stability that will be initiated in Phase I for the final device with each of the different liquid formulations. To be included in the Phase I report is the 30 day accelerated (40°C, 75% relative humidity) stability testing. The testing should be conducted in a manner consistent with the following FDA guidance: Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products.

- A Drug Master File for the device including all liquid formulations, completed to FDA specifications.